

Synopsis

The thesis entitled “*Disorder, Polymorphism and Co-crystal formation in molecular crystals: An in-depth study in terms of weak intra- and intermolecular interactions*” consists of **five chapters**.

Three distinct aspects, disorder, polymorphism and co-crystal formation have been addressed in molecular crystals in terms of intra- and intermolecular interactions involving halogens, weak hydrogen bonds and van der Waals interactions. A basic introductory chapter highlights the importance of these three aspects followed by a foreword to the contents.

Chapter 1 employs *in situ* cryo-crystallization techniques to study the crystal and molecular structures of compounds which are liquids at room temperature.

Section 1.1 deals with the crystal structure analyses of low melting chloro- and bromo-substituted anilines which reveal both the importance of hydrogen bonds and weak interactions involving different halogens. The halogen...halogen interactions are compared with fluorine and iodine substituted compounds to bring out the relevance of both size and polarizability characteristics.

Section 1.2 describes the crystal structures of benzyl derivative compounds utilizing the concept of *in situ* cryo-crystallization. This analysis brings out the correlation between acidity of benzyl derivative compounds with its preference of either a $(sp^2)C-H\cdots\pi$ or $(sp^3)C-H\cdots\pi$ interactions in the crystal packing.

Chapter 2 consists of two sections dealing with the preference of halogen...halogen interactions in supramolecular chemistry.

Section 2.1 discusses a statistically large number of crystal structures in halogen substituted benzanilide compounds. It reveals the importance of hetero halogen $F\cdots X$ (Cl, Br), homo halogen $X\cdots X$ (F, Cl, Br, I), $C-X\cdots\pi$ and $C-H\cdots F$ interactions in terms of their directionality and preferences to complement a primary $N-H\cdots O$ hydrogen bond in directing the three-dimensional supramolecular assembly.

Section 2.2 deals with solvent induced polymorphism which highlights the role of weak interactions in two case studies. The preference and directionality of $C-H\cdots F$ and $Cl\cdots Cl$

interactions lead to dimorphic modifications in case of 3-chloro-*N*-(2-fluorophenyl)benzamide whereas in case of 2-iodo-*N*-(4-bromophenyl)benzamide the interactions are through C-H... π and I...I contacts. Further, the analysis is supported using morphological evidence, DSC (Differential scanning calorimetry) and Powder X-ray diffraction data.

Chapter 3 has three sections, concentrating on disorder and its consequence in crystal structures.

Section 3.1 discusses the apparent shortening of the C(sp³)–C(sp³) bond analysed *via* a variable temperature X-ray diffraction study in racemic 1,1'-binaphthalene-2,2'-diyl diethyl bis(carbonate). Variable temperature single crystal X-ray diffraction studies show that the shortening is entirely due to positional disorder and not due to thermal effects. A supercell formation at T \leq 150 K depicts the formation of a Z'= 2 structure.

Section 3.2 deals with crystal structure analysis of Ethyl-4-(2-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate which clarifies the discrepancy in the higher value of the residual electron density in the literature in terms of positional disorder of fluorine at *ortho* sites. The existence of fluorine atom at the *para* position on the phenyl ring of another isomeric molecule leads to disorder induced conformational polymorphism through the involvement of the ethyl group. The static disorder of ethyl group which is associated with only one molecule (Z'=2) could be resolved at 120 K. This supports the results of the previous section (3.1).

Section 3.3 reports crystal structure analysis of disordered fluorine in benzanilide compounds. The preference of interactions involving fluorine in either *ortho* sites or *meta* sites could be one of the reasons for the positional disorder of both possible sites. With one of the structure showing high Z' value due to differences in the occupancy of disordered fluorine atom. CSD (Cambridge Structural Database) analysis indicates that the percentage of disorder in halogenated crystal structures having halogen atom at either *ortho* site or *meta* site decreases from fluorine to iodine. Further, the analysis points out that the disorder in fluorine containing compounds is mostly localized at the fluorine position whereas for other halogenated disordered structures, the disorder appears at other parts of the molecule.

Chapter 4 discusses co-crystal formation and analysis of intermolecular interactions. It consists of two sections.

Section 4.1 discusses co-crystal formation of nicotinamide with benzoic acid and seven other derivatives by changing the functional group at different positions of benzoic acid. Hydroxyl (-OH) group at 4/3-position of benzoic acid prefers phenol...pyridine synthon when at 2-position it prefers acid...pyridine synthon. The preference of amide anti-catemer over dimer synthon is supported by additional C-H...O hydrogen bonds. In case of 3,5-dinitro-2-hydroxy benzoic acid, the disorder in hydroxyl (-OH) group at *ortho* site leads to salt formation.

Section 4.2 describes co-crystal study of adenine and thymine (AT) as free nucleobases. This result reveals the formation of AT (2:1) complex with both Hoogsteen and “quasi-Watson-Crick” hydrogen bonds. The hydrogen bonded bases using the Hoogsteen and the “quasi-Watson-Crick” interactions generate a hexagonal supramolecular motif. Four water molecules are located inside the hexagonal void of this complex. A high temperature study on the same crystal shows that at 313K, one of the water molecules escapes from the lattice resulting in the small change in unit cell parameters. However, the space group remains the same and the hexagonal void remains unaltered. With further increase in temperature, the crystal deteriorates irreversibly which clearly brings out the importance of water molecule in the molecular recognition of adenine-thymine complex.

Chapter 5 discusses crystal structure analysis of *trans*-atovaquone (antimalarial drug), its new polymorph form including one stereoisomer (*cis*) and five other derivatives with different functional groups. Based on the conformational features of these compounds and the characteristics of the nature of hydrogen bonding and other weak intra and intermolecular interactions, docking studies with cytochrome *bc₁* complex provide valuable insight into the atomistic details of protein-inhibitor interactions. The docking results reveal that atovaquone and its derivatives, owing to their nature of hydrogen bond and the propensity towards the formation of weaker hydrogen bonds involving the chlorine atom as well appear as good candidates for drug evaluation.